Uncovering the mechanisms of exertional dyspnoea in combined pulmonary fibrosis and emphysema

Camila M. Costa[1], J. Alberto Neder[2], Carlos G. Verrastro[3], Marcelle Paula-Ribeiro[1], Roberta Ramos[1], Eloara M. Ferreira[1], Luiz E. Nery[1], Denis E. O'Donnell[2], Carlos A.C. Pereira[1] and Jaquelina Ota-Arakaki[1]

Affiliations: [1]Pulmonary Vascular Disease and Interstitial Lung Disease Services, Division of Respirology, Federal University of Sao Paulo, Sao Paulo, Brazil. [2]Laboratory of Clinical Exercise Physiology and Respiratory Investigation Unit, Queen's University and Kingston General Hospital, Kingston, ON, Canada. [3]Division of Imaging, Federal University of Sao Paulo, Sao Paulo, Brazil.

Correspondence: J. Alberto Neder, 102 Stuart Street, Kingston, Ontario, Canada K7 L 2V6. E-mail: alberto.neder@queensu.ca

@ERSpublications
Exertional dyspnoea is related to poor ventilatory efficiency rather than hypoxaemia or inspiratory constraints in CPFE. Lessening patients' excessive ventilation might prove particularly beneficial to mitigate the burden of this disabling symptom. http://bit.ly/2MRn6az

Cite this article as: Costa CM, Neder JA, Verrastro CG, *et al.* Uncovering the mechanisms of exertional dyspnoea in combined pulmonary fibrosis and emphysema. *Eur Respir J* 2020; 55: 1901319 [https://doi.org/10.1183/13993003.01319-2019].

ABSTRACT The prevailing view is that exertional dyspnoea in patients with combined idiopathic pulmonary fibrosis (IPF) and emphysema (CPFE) can be largely explained by severe hypoxaemia. However, there is little evidence to support these assumptions.

We prospectively contrasted the sensory and physiological responses to exercise in 42 CPFE and 16 IPF patients matched by the severity of exertional hypoxaemia. Emphysema and pulmonary fibrosis were quantified using computed tomography. Inspiratory constraints were assessed in a constant work rate test: capillary blood gases were obtained in a subset of patients.

CPFE patients had lower exercise capacity despite less extensive fibrosis compared to IPF (p=0.004 and 0.02, respectively). Exertional dyspnoea was the key limiting symptom in 24 CPFE patients who showed significantly lower transfer factor, arterial carbon dioxide tension and ventilatory efficiency (higher minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio) compared to those with less dyspnoea. However, there were no between-group differences in the likelihood of pulmonary hypertension by echocardiography (p=0.44). High dead space/tidal volume ratio, low capillary carbon dioxide tension emphysema severity (including admixed emphysema) and traction bronchiectasis were related to a high V'_E/V'_{CO_2} ratio in the more dyspnoeic group. V'_E/V'_{CO_2} nadir >50 (OR 9.43, 95% CI 5.28–13.6; p=0.0001) and total emphysema extent >15% (2.25, 1.28–3.54; p=0.01) predicted a high dyspnoea burden associated with severely reduced exercise capacity in CPFE

Contrary to current understanding, hypoxaemia *per se* is not the main determinant of exertional dyspnoea in CPFE. Poor ventilatory efficiency due to increased "wasted" ventilation in emphysematous areas and hyperventilation holds a key mechanistic role that deserves therapeutic attention.

This article has supplementary material available from erj.ersjournals.com

Received: 30 April 2019 | Accepted after revision: 12 Oct 2019

Introduction

The association of centrilobular and/or paraseptal emphysema in upper lung zones and abnormalities indicative of idiopathic pulmonary fibrosis (IPF) in the lower lobes defines the syndrome of combined pulmonary fibrosis and emphysema (CPFE) [1]. Physiologically, IPF and emphysema conflate to decrease the area for gas exchange; conversely, some of their mechanical effects are in opposition, *i.e.* restriction caused by IPF and hyperinflation induced by emphysema. It follows that CPFE patients characteristically present with low transfer factor of the lung for carbon monoxide (T_{LCO}) and marked desaturation on exertion despite relatively preserved lung volumes [1–3]. Clinically, it has been assumed that their high dyspnoea burden [4] is causally related to a heightened hypoxic drive [5] despite the common observation that there is a large variability of dyspnoea and exercise tolerance in patients showing similar hypoxaemia [6]. Moreover, oxygen supplementation inconsistently improves patients' breathlessness, even at high flows [7]. Thus, understanding the mechanisms of exertional dyspnoea remains an important unmet goal to lessen disability and improve the poor health-related quality of life commonly reported by CPFE patients [8].

In this context, it is noteworthy that both IPF and emphysema are associated with enlarged physiological dead space ventilation (increased ratio of dead space volume (V_D) to tidal volume (V_T)) [9, 10]. In order to maintain alveolar ventilation in face of increased "wasted" ventilation, patients need to generate a higher minute ventilation (V'_E) for a given carbon dioxide output (V'_{CO_2}), *i.e.* they tend to present with poor ventilatory efficiency (high V'_E/V'_{CO_2} ratio) [11]. Moreover, if there is increased chemostimulation and V'_E exceeds V_D/V_T (*i.e.* there is alveolar hyperventilation), arterial carbon dioxide tension (P_{aCO_2}) might be regulated at a lower set-point leading to further ventilatory stimulus [11]. In fact, hypocapnia is a common finding in patients whose ventilatory response to a high V_D/V_T and/or heightened chemostimulation is not hindered by critical mechanical constraints, *e.g.* heart failure [12], pulmonary vascular disease [13] and even mild chronic obstructive pulmonary disease (COPD) [14]. Interestingly, a high V'_E/V'_{CO_2} ratio has long been described in IPF [15], particularly in those who are more dyspnoeic [14]. Paradoxically, because CPFE patients characteristically present with lower operating lung volumes and relatively preserved inspiratory reserves compared to IPF [3], they are in a privileged position to readily increase V'_E in response to a high drive, leading to high V'_E/V'_{CO_2} ratio and worse exertional dyspnoea. Therefore, it seems apparent that there is a strong rationale for a hitherto unexplored link between ventilatory inefficiency and exertional dyspnoea in CPFE.

In this prospective study we aimed to explore this novel research question by contrasting the sensory and physiological adjustments to exercise in CPFE and IPF patients. We hypothesised that there is a significant relationship between higher dyspnoea burden and ventilatory inefficiency in CPFE. Owing to similar exertional hypoxaemia [16], but larger inspiratory reserves in CPFE than IPF, these results would provide evidence that ventilatory inefficiency, rather than hypoxaemia or neuromechanical uncoupling due to hyperinflation [17] is a major determinant of exertional dyspnoea and exercise tolerance in the former group.

Methods

Subjects

58 tobacco smokers or ex-smokers (45 males, aged 58–88 years) presenting with clinical and imaging (high-resolution computed tomography (HRCT)) features of IPF [18] were included. HRCT scans were categorised as "consistent with an usual interstitial pneumonia (UIP) pattern", "probable UIP pattern" or "indeterminate for UIP pattern" according to current recommendations [18]. 42 subjects (the CPFE group) [2–4, 6, 19] presented with emphysema involving >5% of the whole lung volume, whereas the other 16 patients (the IPF group) did not have any evidence of emphysema or, if present, it was within the range of values described in subjects at same age range (⩽3% of the whole lung volume without bullae) [20]. In addition to similar age and sex distribution of the CPFE group, these patients presented with equivalent exercise-induced (or worsened) hypoxaemia in a ramp-incremental cycle cardiopulmonary exercise test (CPET) to symptom-limited peak, *i.e.* same peak oxygen saturation by pulse oximetry (S_{pO_2}) after a similar rest-to-peak decrease in S_{pO_2}. Other inclusion and exclusion criteria and a detailed methodological description are provided in the supplementary material. After written informed consent, subjects underwent, on different days, a ramp-incremental cycle CPET to symptom-limited peak and a constant work rate at 75% peak work rate to the limit of tolerance (minutes). This cross-sectional study received ethical approval from the Federal University of Sao Paulo Hospital's research ethics board (1.368.592-2015) and Queen's University Affiliated Teaching Hospitals research ethics board (DMED-2158-2018).

Procedures

Chronic dyspnoea was assessed by questionnaire (Mahler's baseline dyspnoea index) [21]. Transthoracic echocardiography with continuous-wave Doppler measurements was performed and interpreted according to the standards proposed in 2015 by the European Society of Cardiology and the European Respiratory

Society [22]. Visual chest HRCT quantification of emphysema burden was performed based on Jacob *et al.* [3]. The extent of fibrosis, emphysema and honeycombing were estimated to the nearest 5% on a lobar basis. The lobar scores were adjusted to reflect the physiological contribution of each lobe to the total lung volume as previously characterised by scintigraphic and gas dilution techniques [23].

Spirometry, static lung volumes and single-breath T_{LCO} were performed using automated equipment (1085 ELITE D (Medical Graphics Corp, St. Paul, MN, USA) in Brazil, and Vmax229d (SensorMedics, Yorba Linda, CA, USA) in Canada) following standard technical recommendations. Arterial blood gases and acid–base balance were measured in a sample obtained from the radial artery in standard anaerobic conditions (ABL800 FLEX; Radiometer, Copenhagen, Denmark). V_D/V_T ratio was calculated using the modified Bohr equation (Enghoff's modification) [10].

The exercise tests were conducted on an electronically-braked cycle ergometer (Ergoline 800S; SensorMedics) using a SensorMedics Vmax229d system. Peak oxygen uptake (V'_{O_2}) <50% predicted defined a severe exercise limitation [24]. V'_E–V'_{CO_2} slope and intercept by linear regression and V'_E/V'_{CO_2} nadir were obtained [14]. Dynamic operating lung volumes were calculated from inspiratory capacity (IC) manoeuvres [25] and dyspnoea intensity assessed with the modified 10-point Borg scale every minute [26]. End-inspiratory lung volume (total lung capacity (TLC) −IC)+V_T)/TLC ⩾0.9 established the presence of critically high inspiratory constraints [25], whereas peak dyspnoea/work rate>sample's median plus peak dyspnoea⩾leg discomfort ratings defined a high exertional dyspnoea burden [27]. Capillary blood samples from the earlobe were obtained after application of a vasodilation-inducing emulsion (Finalgon; Sanofi-Aventis, Frankfurt am Main, Germany) in a subset of CPFE patients who accepted an invasive procedure (n=18) and all IPF patients. V_D/V_T ratio was calculated using the modified Bohr equation (Enghoff's modification) using capillary carbon dioxide tension (P_{cCO_2}) instead of P_{aCO_2} [28].

Statistical analysis

The statistical software package used was SPSS Statistics (version 24; IBM, Armonk, NY, USA). Unpaired t-test (or Mann–Whitney test for asymmetrically distributed data) was used to compare between-group differences. For more than two groups, we used one-way ANOVA or Kruskall–Wallis test. Chi-squared testing was used to compare frequencies and categorical variables. The strength of association between selected continuous variables was investigated by Spearman's ρ. Two-way ANOVA with repeated measures were used to compare variables at selected time points during the constant work rate test. Stepwise backward multiple logistic regression analysis determined the independent predictors of a high dyspnoea burden [27] associated with a severely-reduced peak V'_{O_2} in the CPFE group [24]. The probability of a Type I error was set at 5% ($p<0.05$).

Results

Clinical, resting and exercise characteristics: CPFE versus *pulmonary fibrosis*

The CPFE and IPF groups were well matched by anthropometric and demographic characteristics. The majority of patients in both groups (~70%) showed a HRCT pattern "consistent with" or "probable" UIP. The CPFE group had less fibrosis and honeycombing (table 1). There were no between-group differences in key echocardiographic variables ($p=0.44$); of note, ~20% of patients in both groups had a "high" probability of pulmonary hypertension. Peak tricuspid regurgitant velocity (TRV) values in IPF and CPFE patients showing a high probability of pulmonary hypertension were ⩽3.6 m·s^{-1}, *i.e.* only slightly above the 3.4 m·s^{-1} cut-off. None of these patients (nor those with "intermediate" probability) presented with other echocardiographic signs suggestive of pulmonary hypertension [22, 29].

CPFE patients showed better preserved spirometry and static lung volumes, but similar T_{LCO} compared to IPF (table 1). As expected from the inclusion criteria, the two groups had similar resting (table 1) and exercise-induced hypoxaemia (table 2 and figure 1a). Of note, the CPFE group showed significantly lower peak exercise capacity, lower breathing reserve and higher V'_E/V'_{CO_2} nadir, which were associated with steeper V'_E/V'_{CO_2} slope and worse exertional dyspnoea (table 2).

CPFE patients with higher versus *lower dyspnoea burden: at rest*

24 CPFE patients presented with higher exertional dyspnoea burden [30]; they also reported worse dyspnoea in daily life compared to their counterparts (table 1). No echocardiographic variable was associated with dyspnoea burden, including those reflecting potential pulmonary hypertension ($p=0.68$) Although dynamic and static lung volumes and arterial oxygen saturation did not differ between the CPFE groups, more dyspnoeic patients presented with lower transfer factor, lower P_{aCO_2} and higher resting V_D/V_T ratio (table 1).

TABLE 1 Resting characteristics of patients with interstitial pulmonary fibrosis (IPF) alone or in association with emphysema (combined pulmonary fibrosis and emphysema (CPFE))

	IPF	CPFE		
		All patients	Lower dyspnoea burden	Higher dyspnoea burden
Subjects n	16	42	18	24
Demographic/anthropometric/clinical				
Male	12 (75)	33 (78.5)	14 (77.7)	19 (79.1)
Age years	67.8±7.9	69.5±5.1	70.2±4.6	68.8±4.3
Body mass index kg·m^{-2}	27.1±3.0	26.4±3.7	26.8±3.1	25.9±4.3
Smoking pack-years	21±13	43±22	42±19	44±17
Baseline dyspnoea index median (IQR)	10 (2)	8 (2)	10 (2)	6 (2)
Echocardiography				
LV ejection fraction %	63±7	66±8	64±6	67±9
PASP mmHg	33±10	35±8	36±9	34±7
Peak TRV m·s^{-1}	2.2±0.5	2.4±0.4	2.5±0.4	2.3±0.6
Probability of pulmonary hypertension				
High	3 (18.7)	8 (19.0)	4 (22.2)	4 (16.6)
Intermediate	4 (25.0)	10 (23.9)	4 (22.2)	4 (16.6)
Low	10 (62.5)	24 (57.1)	10 (55.6)	16 (66.8)
HRCT				
Pattern of fibrosis				
UIP	10 (62.5)	24 (57.1)	10 (55.5)	14 (58.3)
Probable UIP	3 (18.7)	11 (26.2)	5 (27.7)	6 (25.0)
Indeterminate for UIP	3 (18.8)	7 (16.7)	3 (16.8)	4 (16.7)
Fibrosis extent median (IQR)	35 (10)	25 (15)	25 (10)	25 (10)
TxB moderate–severe	9 (56.2)	20 (47.6)	4 (22.2)	16 (66.6)
Honeycombing % median (IQR)	15.5 (5)	9.0 (5)	8.5 (5)	10.5 (5)
Total emphysema extent % median (IQR)	2 (2)	15 (10)	10 (5)	20 (5)
Total emphysema >15%	0	26 (61.9)	6 (33.3)	20 (83.3)
Admixed emphysema % median (IQR)	2 (2)	60 (85)	45 (40)	80 (55)
Total admixed emphysema >60%	0	26 (61.9)	5 (27.7)	21 (87.5)
Lung function				
FVC % pred	61.3±19.1	85.2±17.9	84.1±14.9	86.7±18.1
FEV_1 % pred	60.9±18.1	86.3±16.9	85.9±15.2	86.9±13.8
FEV_1/FVC	0.88±0.11	0.80±0.09	0.79±0.10	0.82±0.07
TLC % pred	59.1±16.5	78.6±15.7	76.9±12.6	79.3±13.6
Residual volume % pred	64.6±19.0	85.4±21.1	83.0±18.4	86.9±17.4
Inspiratory capacity % pred	61.4±17.6	82.3±16.4	80.7±15.8	83.1±15.7
T_{LCO} % pred	36.6±15.9	34.1±20.1	39.6±13.5	30.8±15.1
FVC/T_{LCO}	1.61±0.48	2.41±0.58	2.11±0.39	2.80±0.41
S_{aO_2} %	92±4	93±3	91±3	92±4
P_{aO_2} mmHg	69±5	70±6	68±4	71±5
$P_{(A\text{-}a)O_2}$ mmHg	26.4±9.7	28.1±13.1	25.2±8.6	31.3±7.4
P_{aCO_2} mmHg	37±4	35±5	38±3	34±3
HCO_3^- mEq·L^{-1}	23.0±2.8	22.1±3.1	24.0±2.9	18.1±2.6
V_D/V_T	0.46±0.08	0.48±0.12	0.45±0.07	0.55±0.06

Data are presented as mean±SD or n (%), unless otherwise stated. The CPFE group was separated according to the severity of exertional dyspnoea. IQR: interquartile range; LV: left ventricular; PASP: pulmonary artery systolic pressure; TRV: tricuspid regurgitant velocity; HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; TxB: traction bronchiectasis; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; T_{LCO}: transfer factor of the lung for carbon monoxide; S_{aO_2}: arterial oxygen saturation; P_{aO_2}: arterial oxygen tension; $P_{(A-a)O_2}$: alveolar–arterial oxygen tension difference; P_{aCO_2}: arterial carbon dioxide tension; HCO_3^-: bicarbonate; V_D: dead space volume; V_T: tidal volume.

CPFE patients with higher versus *lower dyspnoea burden: exercise*

In the incremental test, CPFE patients with higher exertional dyspnoea burden showed significantly lower peak exercise capacity, which was associated with an earlier estimated lactate threshold, lower oxygen pulse, higher V'_E/V'_{CO_2} and lower end-tidal partial pressure for carbon dioxide (P_{ETCO_2}) (table 2 and figure 1). Despite similar hypoxaemia in the constant work-rate test (figure 2a), they showed lower endurance exercise tolerance compared to their counterparts with less dyspnoea and the IPF group (5.1±2.3 min, 7.0±2.1 min and 7.1±1.7 min, respectively; mean difference (95% CI) 1.9 (0.4–3.2) min, 2.2 (0.6–2.9) min and 0.1 (−2.1–2.4) min for CPFE higher *versus* lower dyspnoea burden (p=0.010), CPFE higher dyspnoea

TABLE 2 Physiological and sensory responses to incremental cardiopulmonary exercise testing in patients with interstitial pulmonary fibrosis (IPF) alone or in association with emphysema (combined pulmonary fibrosis and emphysema (CPFE))

	IPF	CPFE		
		All patients	Lower dyspnoea burden	Higher dyspnoea burden
Subjects n	16	42	18	24
Metabolic/cardiovascular				
Work rate % pred	66.9±16.7	56.7±17.8¶	60.3±16.9	49.1±14.7+
V'_{O_2} % pred	69.3±15.4	60.3±19.4¶	64.5±17.2	50.8±18.0+
V'_{O_2} <50% pred	5 (31.2)	24 (57.1)¶	6 (33.3)	18 (75)+
LT % V'_{O_2} max predicted#	48.0±12.0	45.3±13.1	46.9±11.7	39.1±10.4+
Heart rate % pred	90.8±9.4	92.1±10.6	89.4±9.6	94.3±8.4
Oxygen pulse % pred	73.1±14.5	71.3±16.5	73.7±12.5	64.1±10.9+
Ventilatory				
V'_E/MVV	0.63±0.17	0.56±0.16¶	0.53±0.18§	0.66±0.18f
V'_E–V'_{CO_2} slope	36±11	45±16¶	37±14	55±10+
V'_E–V'_{CO_2} intercept	3.0±3.9	2.1±4.4	3.0±2.9	1.8±3.9
V'_E/V'_{CO_2} nadir	39±10	48±16¶	41±13	57±12+
V'_E/V'_{CO_2} nadir >50	4 (25.0)	23 (54.7)¶	3 (16.6)	20 (83.3)
V_T/IC	0.82±0.07	0.76±0.05¶	0.71±0.04	0.78±0.05+
EILV/TLC	0.93±0.04	0.73±0.06¶	0.74±0.05	0.72±0.07
EILV/TLC ⩾0.9	14 (87.5)	11 (26.1)¶	6 (33.3)	5 (20.8)
Gas exchange responses				
P_{ETCO_2} mmHg	30±8	29±9	34±6	25±7+
$P_{(c-ET)CO_2}$ mmHg	5±3	6±3	4±2	8±3+
S_{pO_2} %	81±6	82±5	81±4	82±6
Peak-rest S_{pO_2} %	−9±5	−10±6	−9±7	−8±5
P_{cO_2} mmHg	58±5	59±6	57±5	59±6
$P_{(A-c)O_2}$ mmHg	38.1±10.1	39.9±9.9	36.9±9.1	45.8±8.4+
Sensory responses (Borg scores)				
Dyspnoea scores median (IQR)	5 (1.5)	7 (2)¶	5 (3)	7.5 (2)+
Dyspnoea/work rate median (IQR) Borg unit/W	0.08 (0.02)	0.12 (0.04)¶	0.09 (0.03)	0.17 (0.03)+
Leg effort scores median (IQR)	5 (2)	5 (2)	4 (3)	6 (1.5)
Dyspnoea ⩾ leg effort	8 (50.0)	30 (71.4)¶	6 (33.3)	24 (100)+

Data are presented as mean±SD or n (%) unless otherwise stated. The CPFE group was also separated according to the severity of exertional dyspnoea. Unless otherwise stated, values are at peak exercise. V'_{O_2}: oxygen uptake; LT: estimated lactate threshold; V'_E: minute ventilation; MVV: maximal voluntary ventilation; V'_{CO_2}: carbon dioxide output; V_T: tidal volume; IC: inspiratory capacity; EILV: end-inspiratory lung volume; TLC: total lung capacity; P_{ETCO_2}: end-tidal carbon dioxide tension; $P_{(c-ET)CO_2}$: capillary–end-tidal carbon dioxide tension difference; S_{pO_2}: oxygen saturation measured by pulse oximetry; P_{cO_2}: capillary oxygen tension; $P_{(A-c)O_2}$: alveolar–capillary oxygen tension difference; IQR: interquartile range. #: identified in 10, 23, 9 and 24 subjects in IPF, all CPFE patients, lower dyspnoea CPFE patients and higher dyspnoea CPFE patients, respectively; ¶: p<0.05 CPFE *versus* IPF; +: p<0.05 CPFE with high-dyspnoea burden *versus* other groups; §: p<0.05 both CPFE sub-groups *versus* IPF; f: p<0.05 CPFE with higher dyspnoea burden *versus* CPFE with lower dyspnoea burden.

burden *versus* IPF (p=0.012) and CPFE lower dyspnoea burden *versus* IPF (p=0.88), respectively) (figure 2f). Arterialised blood gas analysis revealed that the higher V'_E/V'_{CO_2} found in the group with higher dyspnoea burden (figure 2b) was associated with higher V_D/V_T (figure 2c) and lower P_{cCO_2} (figure 2d). There were no differences in P_{cO_2} (p=0.64) and inspiratory reserves (p=0.57) comparing the group with higher *versus* lower dyspnoea burden (figure 2). As shown in figure 3, the V'_E/V'_{CO_2} *versus* P_{cCO_2} plot was shifted to the left in the group of patients with higher dyspnoea burden, thereby indicating alveolar hyperventilation; importantly, however, V'_E/V'_{CO_2} was shifted upwards at a given P_{cCO_2} in this group, which is consistent with high "wasted" ventilation [31]. V_D/V_T ratio, V'_E/V'_{CO_2}, P_{ETCO_2} and P_{aCO_2} did not correlate with peak TRV or any of the other echocardiographic signs of potential pulmonary hypertension (p-values 0.32–0.85).

CPFE patients with higher dyspnoea burden: structural correlates

There were no between-group differences in the frequency of specific patterns of fibrosis (p=0.66) (table 1). Higher scores of emphysema (admixed and total) and traction bronchiectasis were found in the more dyspnoeic group (p=0.001 and p=0.01, respectively). Significant correlations were observed between dyspnoea/work rate slope with admixed emphysema (ρ=0.70; p=0.008) and total emphysema extent (ρ=0.66; p=0.015), but not honeycombing (p=0.44). Of note, "moderate to severe" extension of traction bronchiectasis and emphysema extent >15% were significantly more frequent in the more dyspnoeic group compared to their counterparts (p=0.01 and p=0.0012, respectively) (table 1). In fact, total emphysema

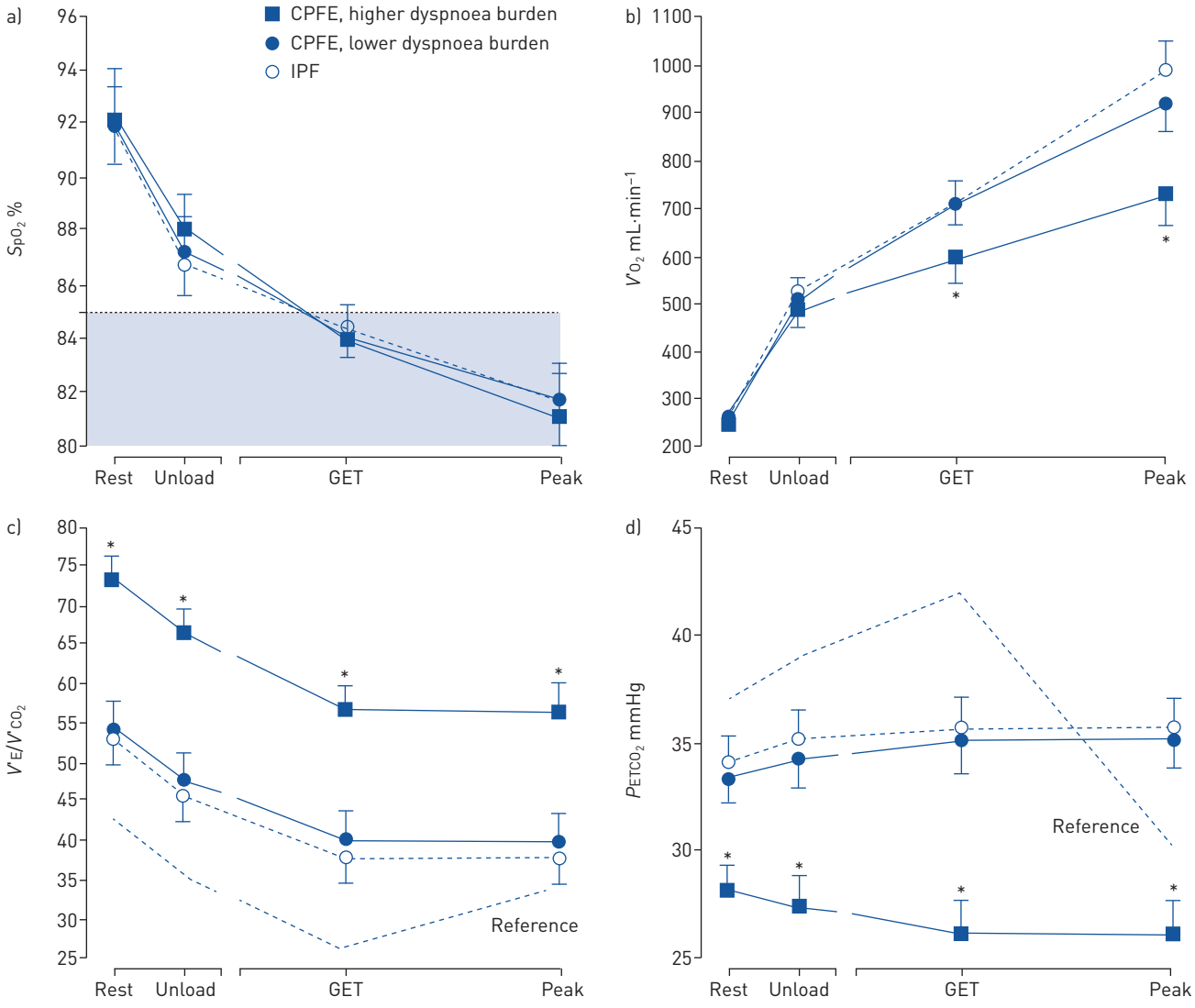

FIGURE 1 a) Oxygen saturation measured by pulse oximetry (S_{pO_2}); b) oxygen uptake (V'_{O_2}); c) ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio; and d) end-tidal partial pressure for carbon dioxide (P_{ETCO_2}) in response to incremental cardiopulmonary exercise testing in patients with idiopathic pulmonary fibrosis (IPF) in isolation or in association with emphysema (combined pulmonary fibrosis and emphysema (CPFE)). The latter group was separated according to the burden of exertional dyspnoea. Shaded area in a) indicates severe exertional hypoxaemia. Reference values are based on laboratory's historical controls. Data are presented as mean±SEM. GET: gas exchange (lactate) threshold. *: p<0.05 CPFE with high dyspnoea burden *versus* other groups.

extent >15% and V'_E/V'_{CO_2} nadir >50 were the only independent predictors of a high exertional dyspnoea burden combined with a severely reduced peak V'_{O_2} in the CPFE group (table 3).

Discussion

This is the first investigation on the mechanisms underlying a key clinical outcome of CPFE: exertional dyspnoea [1]. Our main original findings are 1) CPFE patients with a higher dyspnoea burden presented with the poorest exercise tolerance, which was associated with increased ventilatory response to metabolic demand (poor ventilatory efficiency) despite relatively preserved mechanical-inspiratory reserves; 2) high "wasted" ventilation in the dead space and a low P_{cCO_2}, but not exertional hypoxaemia or critical inspiratory constraints, jointly explained patients' poor ventilatory efficiency; and 3) emphysema (including admixture emphysema) and traction bronchiectasis were the closest structural correlates of a high V_D/V_T ratio, exertional dyspnoea and poor exercise tolerance in the CPFE group. Our results provide the first piece of evidence that physiological sources of ventilatory stimuli that are not necessarily related to the severity of hypoxaemia (increased "wasted" ventilation and chronic hyperventilation) are the key mechanisms underlying exertional dyspnoea in CPFE. Therapeutic strategies focused on improving these

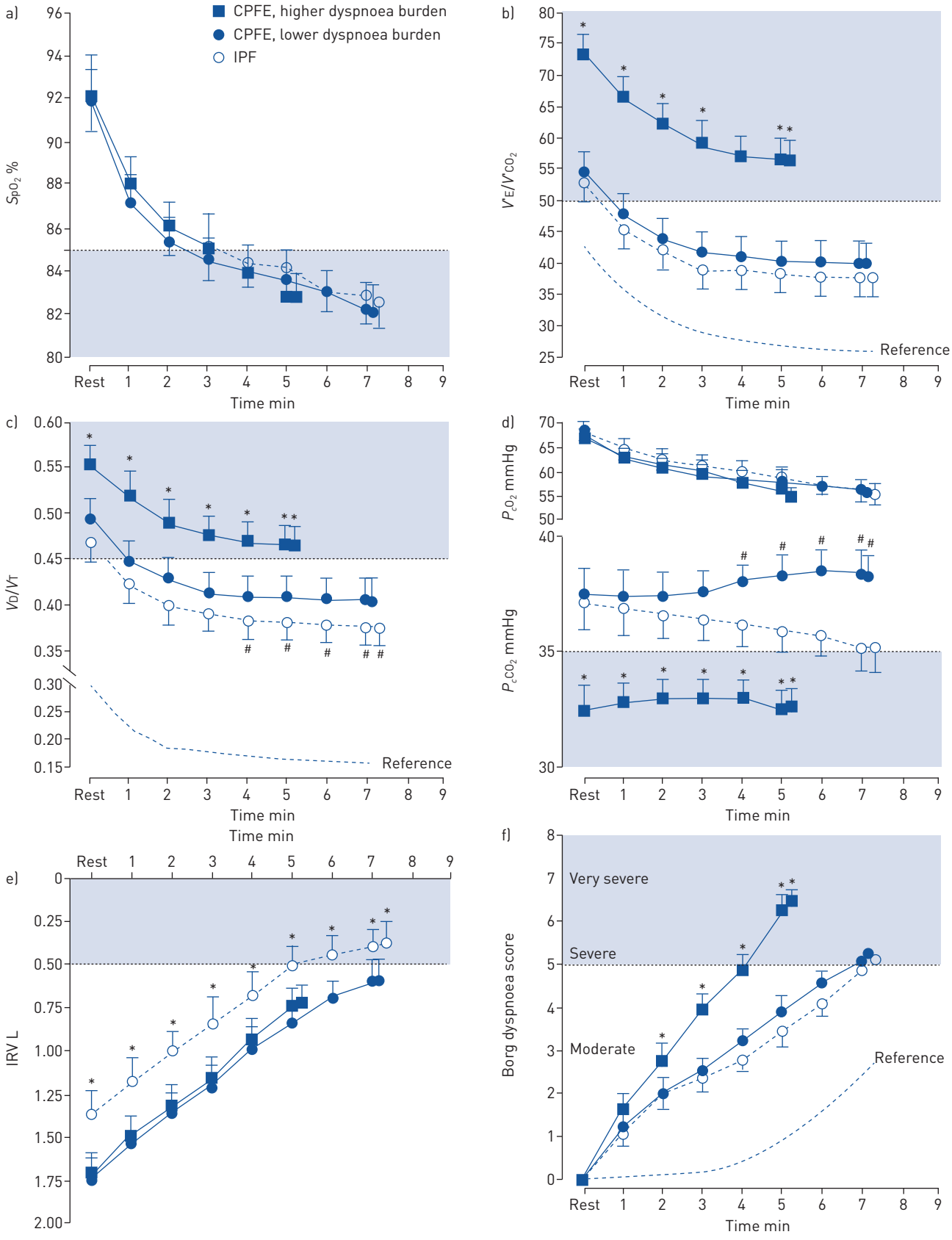

FIGURE 2 a–d) Pulmonary gas exchange, e) mechanical and f) sensory responses to constant work rate cardiopulmonary exercise test to symptom limitation in patients with idiopathic pulmonary fibrosis (IPF) in isolation or in association with emphysema (combined pulmonary fibrosis and emphysema (CPFE)). The latter group was separated according to the burden of exertional dyspnoea. Shaded areas indicate values

commonly associated with disability. Reference values are based on laboratory's historical controls. Data are presented as mean±SEM. *: p<0.05 CPFE with high dyspnoea burden *versus* other groups; #: p<0.05 CPFE with lower dyspnoea burden burden *versus* IPF. S_{pO_2}: oxygen saturation measured by pulse oximetry; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide output; V_D: dead space; V_T: tidal volume; P_{cO_2}: capillary oxygen tension; P_{cCO_2}: capillary carbon dioxide tension; IRV: inspiratory reserve volume.

interrelated pathophysiological phenomena might prove relevant to lessen the burden of this devastating symptom in patients with CPFE.

Ventilatory inefficiency and exertional dyspnoea in CPFE

We confirmed our main original hypothesis that poor ventilatory efficiency (high V'_E/V'_{CO_2}) [32] would emerge as a key functional correlate of exertional breathlessness in CPFE when the confounding effects of hypoxaemia were controlled for [16, 30]. In the present study, a high exertional dyspnoea burden was defined considering its importance relative to leg effort in a given subject and its severity comparative to other patients facing a similar challenge (work rate) [27], *i.e.* we obtained an index of intra- and inter-subject dyspnoea severity [21]. Exertional dyspnoea characteristically increases when the mechanical output of the respiratory muscles becomes uncoupled from increases in neural respiratory drive [33]. This might happen secondary to excessive ventilatory stimulus as reflect by ventilatory–metabolic uncoupling (high V'_E/V'_{CO_2}) and/or the development of critical constraints to V_T expansion (neuromechanical dissociation) [33]. Our observation that the more dyspnoeic CPFE patients (figure 2f) showed the highest V'_E/V'_{CO_2} (figure 2b) which coexisted with increased V_D/V_T (figure 2c) and lower P_{cCO_2} (figure 2d) despite preserved inspiratory reserves (figure 2e) provide support to the notion that heightened ventilatory stimuli (not hypoxaemia (figure 2a) or constrained lung mechanics) largely explained the unduly exertional dyspnoea reported by these patients.

In this context, there is well established evidence that increased dead space ventilation (high V_D/V_T) is a consequence of increased volume of conducting airways (due to dilation or longitudinal growth) [34] and more extensive areas of high ventilation/perfusion ratio in IPF [9], *i.e.* both the anatomical and physiological dead space are increased [35]. A high dead space requires an increase in V'_E to avoid carbon dioxide (CO_2) retention [36]: this is particularly critical under the stress of exercise when there is an increase in the CO_2 flow from the peripheral muscles to the lungs. The coexistence of a high V_D/V_T with a low P_{aCO_2} at rest (table 1) and P_{cCO_2} on exertion (figure 2d) implies that V'_E increased beyond what was required to overcome the "wasted" ventilation in the more dyspnoeic group. Remarkably, the lower resting P_{CO_2} in this group did not change appreciably with exercise, *i.e.* the overhead in V'_E was tightly controlled to maintain it close to its resting set-point (figure 2d). Hypocapnia in our patients may have reflected heightened afferent stimuli from multiple sources, *e.g.* central and peripheral chemoreceptors, sympathetic drive and ergoreceptors, among others [37]. Although it remains to be elucidated what are the precise mechanisms driving hyperventilation in the more dyspnoeic patients, enlarged V_D/V_T may increase the

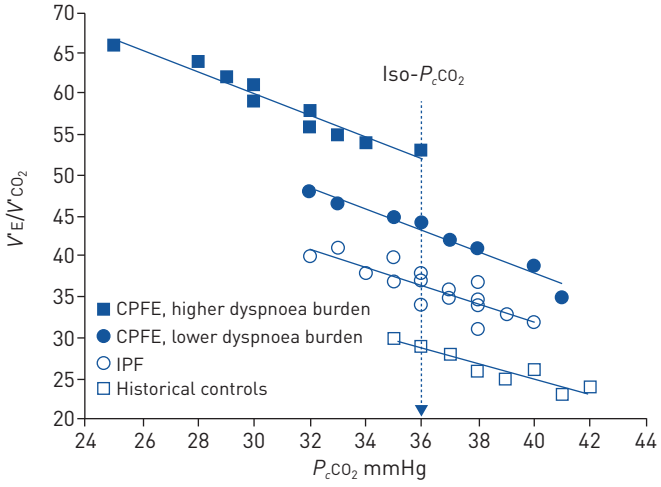

FIGURE 3 Minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio as a function of capillary carbon dioxide tension (P_{cCO_2}) in patients with idiopathic pulmonary fibrosis (IPF) in isolation or in association with emphysema (combined pulmonary fibrosis and emphysema (CPFE)). The latter group was separated according to the burden of exertional dyspnoea. Whereas a leftward shift in P_{cCO_2} associated with high V'_E/V'_{CO_2} indicates alveolar hyperventilation, the upward shift in V'_E/V'_{CO_2} at a given P_{cCO_2} demonstrates increased "wasted" ventilation in the more dyspnoeic patients with CPFE [31].

TABLE 3 Final results of a stepwise backward multiple logistic regression analysis to predict a high dyspnoea burden (dyspnoea/work rate ratio > study population's median value and peak dyspnoea ⩾ leg effort scores) in association with a severely impaired peak oxygen uptake (<50% pred) [24] in patients with combined pulmonary fibrosis and emphysema (CPFE)

	β	OR (95% CI)	p-value	Nagelkerke R^2 % correct
V'_E/V'_{CO_2} nadir >50	2.243	9.43 (5.28–13.6)	0.0001	0.401 (76.8)
Total emphysema extent >15%	0.810	2.25 (1.28–3.54)	0.01	
Constant	−0.191	0.826	0.03	

Other variables in addition to minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) ratio nadir and total emphysema extent considered in the initial multivariable model were "high" or "high plus intermediate" probability of pulmonary hypertension; resting and peak exercise oxygen saturation by pulse oximetry (%), transfer factor of the lung for carbon monoxide (% pred), extent of pulmonary fibrosis (%), forced vital capacity (% pred) or total lung capacity (% pred).

amplitude of intra- and inter-breath CO_2 oscillations thereby stimulating the central chemosensitive neurons [38], particularly in the presence of chronic hypoxaemia [39]. Future studies addressing chemoreceptor sensitivity with hypoxia/hypercapnia tests might provide important insights into this complex issue [40].

It is also noteworthy that V_T increased to a greater extent in the hypocapnic group (table 2). Contrary to patients with "pure" emphysema in whom V_T expansion is usually constrained at high operating lung volumes (leading to hypercapnia) [41], it seems apparent that the restrictive effects of fibrosis allowed greater room for V_T increase in the dyspnoeic patients with CPFE. As a consequence, V_T could readily overcome the enlarged V_D in order to keep P_{aCO_2} at the low level regulated at rest. These findings demonstrated that the operating characteristics of the mechanical plant (the ventilatory pump) have an important influence in the dynamic interactions between the central controller and the chemical/gas exchange plant in human disease [42].

The structural determinants of ventilatory inefficiency in CPFE

We found a noticeable cross-association between dyspnoea burden, high V_D/V_T and high V'_E/V'_{CO_2} with emphysema extent in CPFE. Thus, despite the growing evidence that emphysema extent does not affect mortality beyond the expected from the fibrosis burden [3, 6] the present results show that it does carry an important negative effect on morbidity. For instance, CPFE patients desaturate at similar extent than those with IPF (figure 1a) in spite of showing less extensive fibrosis (table 1). Interestingly, increased wasted ventilation was significantly related to the extent of structural abnormalities signalling for enlarged air spaces, such as emphysema and traction bronchiectasis (table 1). Influential microcomputed tomography studies showed that loss of terminal bronchiole usually precede centrilobular emphysema; centrilobular emphysema is then formed distal to surviving bronchioles, supported by extensive collateral ventilation. Functionally, therefore, they work as areas of high ventilation–perfusion [43]. In an autopsy based study of patients with CPFE, vascular rarefaction was observed near thick-walled cystic lesions representing areas of reticulation adjacent to emphysema [44]. As emphysema and fibrosis frequently coexist in a given lung segment, the traction effects of the latter may further enlarge the dead space effect of emphysematous areas [45]. Although this preserves lung volumes [3], it may have important deleterious effects on ventilation distribution. Thus, vascular destruction might be a consequence of both fibrotic and emphysematous processes in areas of admixed emphysema [45]. Collectively, these results seem to provide support to long-term conjectures that these abnormalities are relatively well ventilated but poorly (or not) perfused, *i.e.* they would work either as "dead space effect" or true dead space units [46]. A note of caution should be made regarding to V_D/V_T by the Bohr–Engoff formulation as hyperventilation may spuriously increase its value [10]. However, the noticeable upward displacement of V'_E/V'_{CO_2} as a function of P_{cCO_2} (figure 3) and the larger positive $P_{(c\text{-}ET)CO_2}$ (table 2) provide supporting evidence that a high V_D/V_T was an important mechanism driving poorer ventilatory efficiency in the more dyspnoeic group with CPFE (figure 2) [31].

It also remains possible that part of the higher V_D/V_T in these patients was related to impaired perfusion of relatively preserved lung parenchyma (as has been described in pulmonary fibrosis [35] and COPD [47]) and/or a predominance of the pulmonary vascular phenotype of COPD. The presence of markers of "impaired oxygen delivery/utilisation" in this group (*e.g.* earlier estimated lactate threshold, lower peak oxygen pulse) (table 2) might reveal worsening pulmonary vasculopathy; however, these findings might

merely reflect the consequences of severe physical inactivity experienced by the most dyspnoeic patients. It should be noted that we were unable to find significant associations between echocardiographic indicators of pulmonary hypertension and ventilatory inefficiency or V_D/V_T in the CPFE patients. The lower prevalence of patients with intermediate or high likelihood of pulmonary hypertension compared to previous studies [48] might reflect the lower summative extents of emphysema and PF in our sample. In fact, T_{LCO} in the range of 20–30% pred is commonly seen in those with higher likelihood of pulmonary hypertension [48]; in contrast, our patients typically showed values >30% pred (table 1). It could be argued that the currently recommended TRV thresholds have limited value in excluding pulmonary hypertension in PF [49]; however, we did not find a single patient with additional echocardiographic signs of pulmonary hypertension. In any case, the relevance of ventilatory inefficiency as a mechanism of exertional dyspnoea might further increase as CPFE progresses as pulmonary hypertension is characteristically associated with increased ventilatory stimulus and high V_D/V_T.

Clinical implications

In order to identify the CPFE patients at higher risk of disablement due to severe exertional dyspnoea, we provided evidence that the physician may rely on selected imaging (high burden of overall and admixed emphysema and traction bronchiectasis) and, in particular, CPET (high V'_E/V'_{CO_2}) variables. Identifying areas of poor pulmonary perfusion relative to ventilation might also prove valuable to identify patients with more extensive wasted ventilation. Although alleviation of exertional hypoxaemia is likely useful to decrease the afferent ventilatory stimuli and improve central haemodynamics, our results indicate that it has a limited potential to improve dyspnoea and exercise tolerance in CPFE. Due to relatively preserved inspiratory reserves (table 2; figure 2e), inhaled bronchodilators are also unlikely to work at the same extent as in COPD. It follows that there is a sounder rationale for strategies to reduce "wasted" ventilation (*e.g.* surgical or bronchoscopic approaches to reduce localised hyperinflation and emphysema) and/or decrease non-hypoxic afferent stimuli (*e.g.* exercise training to lessen ergoreceptor activation and lactic acid production, sympathetic modulation) [31, 50]. If future studies show a role for pulmonary vasculopathy in increasing the "wasted" ventilation in non-emphysematous areas, vasodilators (particular if inhaled to minimise the risk of worsening ventilation–perfusion relationship) might prove beneficial. Acting on the central modulation of the symptom may also be helpful in selected patients, *e.g.* oral or inhaled opiates [31, 50].

Study limitations

Naturally, the present study has some limitations. Due to the complexities involved in a prospective clinical physiology study involving exercise tests a frail population, our sample was necessarily smaller than large imaging-based, retrospective studies [2, 3]. Haemodynamic measurements on exercise might have been useful to confidently rule out exercise-induced pulmonary hypertension, a confounding factor that certainly merits further investigations using invasive CPET. We recognise that by not matching IPF and CPFE groups by resting lung volumes an "advantage" was given to the latter group pertaining to lung mechanics. However, we contend that had we matched the groups by lung volumes (which are characteristically higher in CPFE) [1] IPF patients would be necessarily less hypoxaemic than their counterparts with CPFE. In fact, by showing that a subgroup of CPFE patients had worse dyspnoea than the IPF group despite higher static and operational lung volumes (table 1) on a background of similar hypoxaemia (figures 1a and 2a), our results provided novel insights into the relevance of ventilatory inefficiency to exertional breathlessness in CPFE.

Conclusions

The present study uncovered a hitherto unknown link between ventilatory inefficiency and exertional dyspnoea in CPFE, a key clinical outcome in these patients [1–5]. The heightened ventilatory response to exertion in the more dyspnoeic patients was associated with increased "wasted" ventilation and chronic alveolar hyperventilation, but not the severity of hypoxaemia or the development of inspiratory constraints. A consistent association between ventilatory inefficiency with total and admixed emphysema and traction bronchiectasis, regardless of the likelihood of pulmonary hypertension by echocardiography, indicates that "wasted" ventilation was primarily related to enlarged airspace in these patients. Therapeutic strategies focused in improving ventilatory efficiency and/or lessening hyperventilation might prove particularly valuable to mitigate the devastating consequences of exertional dyspnoea in patients with CPFE.

Support statement: Camila M. Costa received a Doctoral Fellowship from Brazil's Coordenadoria de Aperfeicoamento do Pessoal de Nivel Superior (CAPES). J. Alberto Neder has been funded by a New Clinician Scientist Program from the Southeastern Ontario Academic Medical Association (SEAMO), Canada. The funders had no role in the study design, data collection and analysis, or preparation of the manuscript.

Conflict of interest: None declared.

References

1 Cottin V. The impact of emphysema in pulmonary fibrosis. *Eur Respir Rev* 2013; 22: 153–157.
2 Cottin V, Hansell DM, Sverzellati N, *et al.* Effect of emphysema extent on serial lung function in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2017; 196: 1162–1171.
3 Jacob J, Bartholmai BJ, Rajagopalan S, *et al.* Functional and prognostic effects when emphysema complicates idiopathic pulmonary fibrosis. *Eur Respir J* 2017; 50: 1700379.
4 Sugino K, Ishida F, Kikuchi N, *et al.* Comparison of clinical characteristics and prognostic factors of combined pulmonary fibrosis and emphysema *versus* idiopathic pulmonary fibrosis alone. *Respirology* 2014; 19: 239–245.
5 Papaioannou AI, Kostikas K, Manali ED, *et al.* Combined pulmonary fibrosis and emphysema: the many aspects of a cohabitation contract. *Respir Med* 2016; 117: 14–26.
6 Ryerson CJ, Hartman T, Elicker BM, *et al.* Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest* 2013; 144: 234–240.
7 Zhang L, Zhang C, Dong F, *et al.* Combined pulmonary fibrosis and emphysema: a retrospective analysis of clinical characteristics, treatment and prognosis. *BMC Pulm Med* 2016; 16: 137.
8 Tomioka H, Mamesaya N, Yamashita S, *et al.* Combined pulmonary fibrosis and emphysema: effect of pulmonary rehabilitation in comparison with chronic obstructive pulmonary disease. *BMJ Open Respir Res* 2016; 3: e000099.
9 Agustí AG, Roca J, Gea J, *et al.* Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1991; 143: 219–225.
10 Robertson HT. Dead space: the physiology of wasted ventilation. *Eur Respir J* 2015; 45: 1704–1716.
11 Whipp BJ. The hyperpnea of dynamic muscular exercise. *Exerc Sport Sci Rev* 1977; 5: 295–311.
12 Wensel R, Georgiadou P, Francis DP, *et al.* Differential contribution of dead space ventilation and low arterial pCO_2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004; 93: 318–323.
13 Mélot C, Naeije R. Pulmonary vascular diseases. *Compr Physiol* 2011; 1: 593–619.
14 Vainshelboim B, Oliveira J, Fox BD, *et al.* The prognostic role of ventilatory inefficiency and exercise capacity in idiopathic pulmonary fibrosis. *Respir Care* 2016; 61: 1100–1109.
15 Marciniuk DD, Watts RE, Gallagher CG. Dead space loading and exercise limitation in patients with interstitial lung disease. *Chest* 1994; 105: 183–189.
16 Harris-Eze AO, Sridhar G, Clemens RE, *et al.* Role of hypoxemia and pulmonary mechanics in exercise limitation in interstitial lung disease. *Am J Respir Crit Care Med* 1996; 154: 994–1001.
17 Mahler DA, O'Donnell DE. Recent advances in dyspnea. *Chest* 2015; 147: 232–241.
18 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
19 Choi SH, Lee HY, Lee KS, *et al.* The value of CT for disease detection and prognosis determination in combined pulmonary fibrosis and emphysema (CPFE). *PLoS One* 2014; 9: e107476.
20 Lynch DA, Austin JHM, Hogg JC, *et al.* CT-definable subtypes of chronic obstructive pulmonary disease: a statement of the Fleischner Society. *Radiology* 2015; 277: 192–205.
21 Mahler DA, Weinberg DH, Wells CK, *et al.* The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.
22 Galiè N, Humbert M, Vachiery J-L, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). *Eur Respir J* 2015; 46: 903–975.
23 Pierce RJ, Brown DJ, Denison DM. Radiographic, scintigraphic, and gas-dilution estimates of individual lung and lobar volumes in man. *Thorax* 1980; 35: 773–780.
24 Jones NL, Makrides L, Hitchcock C, *et al.* Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985; 131: 700–708.
25 Guenette JA, Chin RC, Cory JM, *et al.* Inspiratory capacity during exercise: measurement, analysis, and interpretation. *Pulm Med* 2013; 2013: 956081.
26 Borg G. A category scale with ratio properties for intermodal and interindividual comparisons. *In*: Geissler HG, Petzold P, eds. Psychophysical Judgment and the Process of Perception. Berlin, VEB Deutscher Verlag der Wissenschaften, 1982; pp. 25–34.
27 Neder JA, Berton DC, Marillier M, *et al.* Inspiratory constraints and ventilatory inefficiency are superior to breathing reserve in the assessment of exertional dyspnea in COPD. *COPD* 2019; 16: 174–181.
28 Rocha A, Arbex FF, Sperandio PA, *et al.* Excess ventilation in chronic obstructive pulmonary disease-heart failure overlap. Implications for dyspnea and exercise intolerance. *Am J Respir Crit Care Med* 2017; 196: 1264–1274.
29 Rudski LG, Lai WW, Afilalo J, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713.
30 Du Plessis JP, Fernandes S, Jamal R, *et al.* Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. *Respirology* 2018; 23: 392–398.
31 Naeije R, Faoro V. The great breathlessness of cardiopulmonary diseases. *Eur Respir J* 2018; 51: 1702517.
32 Neder JA, Arbex FF, Alencar MCN, *et al.* Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J* 2015; 45: 377–387.
33 Jolley C, Luo Y, Steier J, *et al.* Neural respiratory drive and symptoms that limit exercise in chronic obstructive pulmonary disease. *Lancet* 2015; 385: Suppl. 1, S51.
34 Plantier L, Debray M-P, Estellat C, *et al.* Increased volume of conducting airways in idiopathic pulmonary fibrosis is independent of disease severity: a volumetric capnography study. *J Breath Res* 2016; 10: 016005.
35 Plantier L, Cazes A, Dinh-Xuan A-T, *et al.* Physiology of the lung in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2018; 27: 170062.
36 Wagner PD. Gas exchange in chronic pulmonary disease. *Clin Physiol* 1985; 5: Suppl. 3, 9–17.
37 Dempsey JA, Smith CA. Pathophysiology of human ventilatory control. *Eur Respir J* 2014; 44: 495–512.
38 Bruce EN, Cherniack NS. Central chemoreceptors. *J Appl Physiol* 1987; 62: 389–402.

39 Smith CA, Forster HV, Blain GM, *et al.* An interdependent model of central/peripheral chemoreception: evidence and implications for ventilatory control. *Respir Physiol Neurobiol* 2010; 173: 288–297.
40 Farina S, Bruno N, Agalbato C, *et al.* Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2018; 259: 178–182.
41 O'Donnell DE, D'Arsigny C, Fitzpatrick M, *et al.* Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am J Respir Crit Care Med* 2002; 166: 663–668.
42 Poon C-S, Tin C. Mechanism of augmented exercise hyperpnea in chronic heart failure and dead space loading. *Respir Physiol Neurobiol* 2013; 186: 114–130.
43 Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* 2004; 364: 709–721.
44 Inomata M, Ikushima S, Awano N, *et al.* An autopsy study of combined pulmonary fibrosis and emphysema: correlations among clinical, radiological, and pathological features. *BMC Pulm Med* 2014; 14: 104.
45 Strickland NH, Hughes JM, Hart DA, *et al.* Cause of regional ventilation-perfusion mismatching in patients with idiopathic pulmonary fibrosis: a combined CT and scintigraphic study. *AJR Am J Roentgenol* 1993; 161: 719–725.
46 Holland RA. Physiologic dead space in the Hamman-Rich syndrome. Physiologic and clinical implications. *Am J Med* 1960; 28: 61–68.
47 Barr RG. The epidemiology of vascular dysfunction relating to chronic obstructive pulmonary disease and emphysema. *Proc Am Thorac Soc* 2011; 8: 522–527.
48 Jacob J, Bartholmai BJ, Rajagopalan S, *et al.* Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema. *Respirology* 2018; 23: 593–599.
49 Keir GJ, Wort SJ, Kokosi M, *et al.* Pulmonary hypertension in interstitial lung disease: limitations of echocardiography compared to cardiac catheterization. *Respirology* 2018; 23: 687–694.
50 O'Donnell DE, Neder JA, Harle I, *et al.* Chronic breathlessness in patients with idiopathic pulmonary fibrosis: a major challenge for caregivers. *Expert Rev Respir Med* 2016; 10: 1295–1303.